

PCT

**NOTIFICATION OF THE RECORDING
OF A CHANGE**

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

Freehills Carter Smith & Beadle
101 Collins Street
Melbourne, VIC 3000
AUSTRALIE

Date of mailing (day/month/year) 16 June 2000 (16.06.00)	
Applicant's or agent's file reference 40137363-1 check 1Ba1370,2905	IMPORTANT NOTIFICATION
International application No. PCT/AU99/00735	International filing date (day/month/year) 08 September 1999 (08.09.99)

1. The following indications appeared on record concerning: <input type="checkbox"/> the applicant <input type="checkbox"/> the inventor <input checked="" type="checkbox"/> the agent <input type="checkbox"/> the common representative		
Name and Address JONES, Paul Freehills Patent Attorneys Level 47 101 Collins Street Melbourne, VIC 3000 Australia	State of Nationality	State of Residence
	Telephone No. 03 9288 1577	
	Facsimile No. 03 9288 1567	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: <input type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence		
Name and Address JONES, Paul Freehills Carter Smith & Beadle 101 Collins Street Melbourne, VIC 3000 Australia	State of Nationality	State of Residence
	Telephone No. 03 9288 1577	
	Facsimile No. 03 9288 1567	
	Teleprinter No.	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to: <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the International Preliminary Examining Authority </div> <div> <input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other: </div> </div>		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Christine Carrié Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 May 2000 (09.05.00)	Applicant's or agent's file reference 40137363-1 check 1Ba0350,2300
International application No. PCT/AU99/00735	Priority date (day/month/year) 11 September 1998 (11.09.98)
International filing date (day/month/year)	08 September 1999 (08.09.99)
Applicant ABRAM, Albert, Zorko	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

04 April 2000 (04.04.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38
--	--

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

DEMAND

CHAPTER II

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
Applicant's or agent's file reference 40137363	
International application No. PCT/AU99/00735	International filing date (day/month/year) 08 September 1999 08/09/99
(Earliest) Priority date (day/month/year) 11 September 1998 11/09/98	
Title of invention MOUSSE COMPOSITION	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) SOLTEC RESEARCH PTY LTD 8 Macro Court Rowville, Victoria 3178 AUSTRALIA	
Telephone No.:	
Facsimile No.:	
Teleprinter No.:	
State (that is, country) of nationality: AUSTRALIA	State (that is, country) of residence: AUSTRALIA
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ABRAM, Albert, Zorko 3 Abbey Court Wantirna, Victoria 3152 AUSTRALIA	
State (that is, country) of nationality: AUSTRALIA	State (that is, country) of residence: AUSTRALIA
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) 	
State (that is, country) of nationality:	State (that is, country) of residence:
<input type="checkbox"/> Further applicants are indicated on a continuation sheet.	

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in-addition to the agent(s)/common representative appointed earlier.

Name and address: (Family name followed by given name; for a legal entity, full official designation.
 The address must include postal code and name of country.)

NOONAN, Greg
 CHERRY, James
 DI GIANTOMASSO, Frank
 CALLINAN, Keith
 JONES, Paul
 DAVY, John
 TULLOCH, Debra

Freehills Patent Attorneys
 Level 47
 101 Collins Street
 Melbourne, Victoria 3000
 AUSTRALIA

Telephone No.:

(613) 9288 1577

Facsimile No.:

(613) 9288 1567

Teleprinter No.:

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION**Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

- ☒ the international application as originally filed
- the description ☐ as originally filed
☐ as amended under Article 34
- the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34
- the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

- ☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary application.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | | |
|----|---|---|--------|
| 1. | translation of international application | : | sheets |
| 2. | amendments under Article 34 | : | sheets |
| 3. | copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. | copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. | letter | : | sheets |
| 6. | other (<i>specify</i>) | : | sheets |

For International Preliminary Examining Authority use only

received	not received
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. <input type="checkbox"/> fee calculation sheet | 4. <input type="checkbox"/> statement explaining lack of signature |
| 2. <input type="checkbox"/> separate signed power of attorney | 5. <input type="checkbox"/> nucleotide and or amino acid sequence listing in computer readable form |
| 3. <input type="checkbox"/> copy of general power of attorney; reference number if any | 5. <input type="checkbox"/> other (<i>specify</i>): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



.....
Greg NOONAN, for and on behalf of the applicants

For International Preliminary Examining Authority use only

- | | |
|--|---|
| 1. Date of actual receipt of DEMAND: | |
| 2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b): | |
| 3. <input type="checkbox"/> The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. | <input type="checkbox"/> The applicant has been informed accordingly. |
| 4. <input type="checkbox"/> The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5. | |
| 5. <input type="checkbox"/> Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | |

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Demand received from IPEA on:

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 40137363	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. PCT/AU99/00735	International filing date (<i>day/month/year</i>) 8 September 1999	Priority Date (<i>day/month/year</i>) 11 September 1998
International Patent Classification (IPC) or national classification and IPC Int. Cl. ⁷ A61K 009/12		
Applicant SOLTEC RESEARCH PTY LTD et al		

1.	This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2.	This REPORT consists of a total of 3 sheets, including this cover sheet. <input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheet(s).
3.	This report contains indications relating to the following items: I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 4 April 2000	Date of completion of the report 10 July 2000
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer G.R.PETERS Telephone No. (02) 6283 2184

I. Basis of the report

1. With regard to the elements of the international application:*
- ☒ the international application as originally filed.
- ☐ the description, pages , as originally filed,
 pages , filed with the demand,
 pages , received on with the letter of
- ☐ the claims, pages , as originally filed,
 pages , as amended (together with any statement) under Article 19,
 pages , filed with the demand,
 pages , received on with the letter of
- ☐ the drawings, pages , as originally filed,
 pages , filed with the demand,
 pages , received on with the letter of
- ☐ the sequence listing part of the description:
 pages , as originally filed
 pages , filed with the demand
 pages , received on with the letter of
2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:
- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, was on the basis of the sequence listing:
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished
4. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/fig.
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims 3,4,8,12,13,17	YES
	Claims 1,2,5-7,9-11,14-16,18-21	NO
Inventive step (IS)	Claims 3,4,8,12,13,17	YES
	Claims 1,2,5-7,9-11,14-16,18-21	NO
Industrial applicability (IA)	Claims 1-21	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

NOVELTY (N) and INVENTIVE STEP (IS) Claims 1,2,5-7,9-11,14-16,18-21.

- WO 9325189


The citation, at example 1 (page 6) clearly discloses a pharmaceutical aerosol composition including:

- a pharmaceutically active ingredient (Silver Sulfadiazine)
- an occlusive agent (White Petrolatum)
- an aqueous solvent (water)
- an organic cosolvent (Stearyl alcohol)

Clearly claim 1 is not novel and lacks an inventive step. This and the following examples also disclose the features added by the other abovementioned claims rendering these not novel and non-inventive also.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00735

A. CLASSIFICATION OF SUBJECT MATTER		
Int Cl ⁶ : A61K 009/12		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) IPC A61K 009/12		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU: IPC AS ABOVE.		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) FILE WPAT (DERWENT ABSTRACTS) FILE CAPLUS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9325182 A (Ballard Pharmaceutical Products) 23 December 1993, Pages 6-7	1-21
P,X	WO 9904751 A (Unilever PLC) 4 February 1999, Page 16	1-21
P,X	GB 2327344 A (Ninh Thuy On) 27 January 1999, Pages 3-4	1-21
<input type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex		
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>		
Date of the actual completion of the international search 14 October 1999		Date of mailing of the international search report 21 OCT 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929		Authorized officer  G.R.PETERS Telephone No.: (02) 6283 2184

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU 99/00735

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member		
W9325189	EP644753	US5143717	AU22677/92
			END OF ANNEX

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/12	A1	(11) International Publication Number: WO 00/15193 (43) International Publication Date: 23 March 2000 (23.03.00)
(21) International Application Number: PCT/AU99/00735 (22) International Filing Date: 8 September 1999 (08.09.99) (30) Priority Data: PP 5831 11 September 1998 (11.09.98) AU (71) Applicant (for all designated States except US): SOLTEC RESEARCH PTY LTD [AU/AU]; 8 Macro Court, Rowville, VIC 3178 (AU). (72) Inventor; and (75) Inventor/Applicant (for US only): ABRAM, Albert, Zorko [AU/AU]; 3 Abbey Court, Wantima, VIC 3152 (AU). (74) Agents: JONES, Paul et al.; Freehills Patent Attorneys, Level 47, 101 Collins Street, Melbourne, VIC 3000 (AU).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: MOUSSE COMPOSITION (57) Abstract A pharmaceutical aerosol foam composition including an effective amount of a pharmaceutically active ingredient; an occlusive agent; an aqueous solvent; and an organic cosolvent, the pharmaceutically active ingredient being insoluble in both water and the occlusive agent; the occlusive agent being present in an amount sufficient to form an occlusive layer on the skin, in use.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
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CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

MOUSSE COMPOSITION

The present invention provides a composition for the topical administration of pharmaceutical active ingredients.

Various aerosol and non-aerosol quick breaking and slow breaking foams for the topical delivery of pharmaceutical active ingredients are known in the prior art. In particular, the foam composition is an aqueous emulsion system. The foam composition upon actuation produces a stabilised, homogeneous, expandable foam which breaks easily with shear. A composition of this type is often referred to as an aerosol foam or "mousse".

It is known to use mousse compositions to topically deliver pharmaceutical active ingredients. An example of such a composition is in Australian patent application 80257/87 which discloses a mousse composition for the topical delivery of the pharmaceutically active ingredient, minoxidil. However the efficiency of such systems to deliver pharmaceutically active ingredients is limited.

Moreover, the majority of topical lotions and creams known or suggested in the prior art for delivering pharmaceutically active ingredients contain large amounts of petrolatum or some other occlusive agent to act as a barrier over the skin. This barrier reduces the evaporation of moisture from the skin which leads to increased moisture in the stratum corneum and in the epidermis and enhances the topical delivery of the pharmaceutical active ingredients.

However, in practice it would not be desirable to include such large amounts of an occlusive agent in a mousse formulation because when dispensed the mousse formulation would be a less stable foam, and upon application, the occlusive agent would leave a greasy, sticky lather on the skin which would not be considered acceptable to the consumer.

In prior art United States patents 5,002,680 and 4,981,677, there is disclosed mousse compositions that contain an occlusive agent such as petrolatum. These compositions are directed towards cosmetic purposes, and

provide no disclosure on their suitability or otherwise to enhance the topical delivery of pharmaceutical active ingredients. Further, in respect of United States Patent 4,981,677 the formulation includes a starch component. It is accordingly not apparent that an occlusive layer would be formed.

Accordingly, it would be a significant advance in the art if a mousse composition could be provided that enhanced the topical delivery of the pharmaceutical active ingredient while preferably still providing a pharmaceutically elegant and consumer acceptable composition.

In a first aspect of the present invention there is provided a pharmaceutical aerosol foam composition including an effective amount of

- a pharmaceutically active ingredient
- an occlusive agent
- an aqueous solvent; and
- an organic cosolvent;

the pharmaceutically active ingredient being insoluble in both water and the occlusive agent;

the occlusive agent being present in an amount sufficient to form an occlusive layer on the skin, in use.

The present invention is predicated on the surprising discovery that a mousse formulation with a relatively low amount of an occlusive agent is still able to reduce trans epidermal water loss and hence in theory increase skin permeability to effect greater drug skin penetration while remaining an elegant and consumer acceptable composition.

The water-insoluble pharmaceutically active ingredient may be any suitable type. An analgesic such as capsaicin or piroxicam, antifungal such as clotrimazole or miconazole nitrate, antibacterial such as nitrofurazone or gramcidin, anaesthetic such as benzocaine or lidocaine, antiviral such as aciclovir or penciclovir, antipruritic such as crotamiton or phenol, antihistamine such as chlorpheniramine or triprolidine, xanthine such as caffeine, sex hormone such as oestradiol or testosterone, anti-inflammatory agent or corticosteroid may be used.

A corticosteroid is preferred. The corticosteroids may be selected from one or more of the group consisting of, betamethasone valerate and clobetasol propionate.

Clobetasol propionate is preferred.

The pharmaceutically active ingredient may be present in any effective amounts. The pharmaceutically active ingredient may be present in amounts of approximately 0.005% by weight to approximately 10% by weight, preferably approximately 0.05% to approximately 1% by weight, based on the total weight of the pharmaceutical aerosol foam composition.

The aerosol foam base can be made using compositions that are well known in the art.

The pharmaceutical aerosol foam composition may further include an effective amount of an aerosol propellant. The aerosol propellant used in the mousse composition may be any suitable gas, such as a hydrocarbon, e.g. propane, butane, CFCs, HFCs, nitrogen or air. In a preferred embodiment the aerosol propellant is a hydrocarbon. Where the aerosol propellant is a hydrocarbon it may be present in an amount of from approximately 2.5% to 20% by weight, preferably 2.5% to 7.5% by weight, based on the total weight of the pharmaceutical mousse composition. The propellant may be introduced into the mousse composition at the time of filling utilising for example a standard aerosol dispenser, e.g. a spray can arrangement.

The occlusive agent utilised in the pharmaceutical composition according to the present invention may be any excipient or combination thereof that provides an occlusive layer or hydration barrier to the skin. An occlusive layer or hydration barrier is a layer or barrier sufficient to result in reduction in trans epidermal water loss, which results in skin hydration. Suitable occlusive agents may be selected from one or more of the group consisting of mineral oils and greases, long chain acids, animal fats and greases, vegetable fats and greases, water insoluble polymers and the like. In a preferred embodiment the occlusive agent is

petrolatum.

The occlusive agent is present in an amount sufficient to permit the formation of an occlusive layer or hydration barrier on the skin of the patient. Surprisingly applicants have discovered it is possible to form such an occlusive layer with a relatively low amount of occlusive agent. For example the amount of occlusive agent in the mousse composition may be up to approximately 55%, preferably approximately 40% or less by weight based on the total weight of the composition. In a preferred embodiment of the invention the amount of occlusive agent in the mousse composition may be up to approximately 50%, more preferably from approximately 20 to 50% by weight.

The pharmaceutical mousse composition may further include an effective amount of an emulsifier and/or surfactant.

The emulsifier or surfactant may be selected from one or more of the group consisting of non-ionic, anionic and cationic surfactants, e.g. fatty alcohols, fatty acids and fatty acid salts thereof.

Suitable emulsifiers or surfactants include pharmaceutically acceptable, non-toxic, non-ionic, anionic and cationic surfactants. Examples of suitable non-ionic surfactants include glycerol fatty acid esters such as glycerol monostearate, glycol fatty acid esters such as propylene glycol monostearate, polyhydric alcohol fatty acid esters such as polyethylene glycol (400) monooleate, polyoxyethylene fatty acid esters such as polyoxyethylene (40) stearate, polyoxyethylene fatty alcohol ethers such as polyoxyethylene (20) stearyl ether, polyoxyethylene sorbitan fatty acid esters such as polyoxyethylene sorbitan monostearate, sorbitan esters such as sorbitan monostearate, alkyl glycosides such as cetearyl glucoside, fatty acid ethanolamides and their derivatives such as the diethanolamide of stearic acid, and the like. Examples of suitable anionic surfactants are soaps including alkali soaps, such as sodium, potassium and ammonium salts of aliphatic carboxylic acids, usually fatty acids, such as sodium stearate. Organic amine soaps, also included, include organic amine salts of aliphatic carboxylic acids, usually fatty acids, such as triethanolamine stearate. Another class of

suitable soaps is the metallic soaps, salts of polyvalent metals and aliphatic carboxylic acids, usually fatty acids, such as aluminium stearate. Other classes of suitable anionic surfactants include sulfated fatty acid alcohols such as sodium lauryl sulfate, sulfated oils such as the sulfuric ester of ricinoleic acid disodium salt, and sulfonated compounds such as alkyl sulfonates including sodium cetane sulfonate, amide sulfonates such as sodium N-methyl-N-oleyl laurate, sulfonated dibasic acid esters such as sodium dioctyl sulfosuccinate, alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate, alkyl naphthalene sulfonates such as sodium isopropyl naphthalene sulfonate, petroleum sulfonate such as aryl naphthalene with alkyl substitutes. Examples of suitable cationic surfactants include amine salts such as octadecyl ammonium chloride, quaternary ammonium compounds such as benzalkonium chloride.

Surfactants which are a mixture of sorbitan monostearate and polysorbate 60 are preferred.

The emulsifier component may be present in any suitable stabilising amount. Preferably the emulsifier component may be in an amount where the ratio of emulsifier component to the occlusive agent, active pharmaceutical ingredient and cosolvent is about 1:5. The emulsifier component may be present in an amount of from approximately 1% to 15% by weight, preferably approximately 2.0% to 5.0% by weight, based on the total weight of the pharmaceutical mousse composition.

The aqueous solvent may be present in an amount of from approximately 25% to 95% by weight, preferably approximately 70% to 85% by weight, based on the total weight of the pharmaceutical mousse composition.

The composition further includes an organic cosolvent. The organic solvent may be an ester of a fatty acid for example a C12 – C15 alkyl benzoate, a medium to long chain alcohol, an aromatic and/or alkyl pyrrolidinone, an aromatic and/or alkyl, and/or cyclic ketone, an aromatic and/or alkyl, and/or cyclic ether, substituted and/or unsubstituted single or multiple ring aromatic, straight chain and/or branched chain and/or cyclic alkane or silicone. The organic cosolvent may

be present in amounts of approximately 0.25% to 50% by weight, preferably 0.5 to 2% by weight, based on the total weight of the pharmaceutical mousse composition. Preferred organic cosolvents include C12 – C15 alkyl benzoates (FINSOLV TN) and caprylic/capric triglyceride (CRODAMOL GTCC).

The pharmaceutical mousse composition according to the present invention may also contain other non-essential ingredients. The composition may contain up to 10 weight percent of conventional pharmaceutical adjuvants. These adjuvants or additives include preservatives, stabilisers, antioxidants, pH adjusting agents, skin penetration enhancers, and viscosity modifying agents.

EXAMPLES

The present invention will now be more fully described with reference to the accompanying figures and examples. It should be understood that the description following is illustrative only and should not be taken in any way as restrictive on the generality of the foregoing description.

Figure 1 illustrates the effect of petrolatum content on in vitro epidermal penetration of clobetasol from topical mousse formulations 72 hours after application of 10mg/cm² of formulation.

Figure 2 illustrates the effect of petrolatum content on the rate of transepidermal water loss (TEWL) determined on the forearm of a healthy volunteer 30 and 120 minutes after topical application of 10mg/cm² of formulation.

Figure 3 illustrates relative decreases in the rate of transepidermal water loss (TEWL) observed on the forearm of a healthy volunteer with increasing concentrations of petrolatum in topically applied formulations.

Figure 4 illustrates the effect of application of a 50% petrolatum mousse formulation on the relative rate of TEWL on the forearm of healthy volunteers (mean±SD, n=6).

Example 1: Formulations

A series of 7 pharmaceutical formulations were prepared in accordance with the present invention. The composition of each formulation is given in Table 1.

Table 1

Ingredient	1	2	3	4	5	6	7
Petrolatum	10%	10%	20%	30%	30%	40%	50%
Clobetasol Propionate	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%
Caprylic/Capric Triglyceride	-	-	-	-	10%	-	-
Alkyl Benzoate	10%	10%	10%	10%	-	10%	10%
Cetearyl glucoside	2.5%	-	-	-	-	-	-
Sorbitan Stearate	-	1.63%	2.54%	3.44%	3.02%	4.35%	5.25%
Polysorbate 60	-	2.37%	3.46%	4.56%	4.98%	5.65%	6.75%
Water	72.25 %	70.95 %	58.95 %	46.95 %	46.95 %	34.95 %	22.95 %
Preservatives	0.2%	-	-	-	-	-	-
Propellant	5%	5%	5%	5%	5%	5%	5%

Example 2: Effect of Petrolatum Concentration on the In-vitro Epidermal Penetration of Clobetasol from Topical Mousse Formulations

Aim

The aim of the study was to:

- (1) determine the penetration of the steroid clobetasol into human epidermis following topical application of mousse formulations to which increasing concentrations of petrolatum had been included as a potential occlusive agent and penetration enhancer.

- (2) To assess clobetasol penetration following application to intact epidermis and that which had been stripped 3 times with tape to model the impaired stratum corneum barrier function seen in the dermatological conditions for which the drug is used clinically.

Method

Preparation of epidermal membranes: Donated human female abdominal skin was separated by blunt dissection, to remove subcutaneous fat and extraneous tissue, and immersed in water at 60°C for 2 minutes to allow separation of the epidermal-dermal junction. Epidermal membranes were lifted from the dermis by gently rolling from one end with the fingers and stored on filter paper, stratum corneum uppermost, at -20°C until use.

Diffusion Studies Epidermal membranes were mounted, stratum corneum uppermost and facing the donor chamber, on filter paper between the two halves of standard horizontal glass Franz-type diffusion cells (area approx. 1.3cm²). The bottom half of the diffusion cells was filled with approximately 3.5ml of receptor medium (either 20% ethanol in distilled water for intact epidermal membrane studies or Baxter 20% Intralipid® solution for stripped skin studies) and continuously stirred with small magnetic fleas. Assembled cells were semi-submerged in a water bath maintained at 35±0.1°C.

Mousse formulations containing 0.05% clobetasol with the inclusion of 0, 30 or 50% petrolatum were gently applied to the donor chamber with a round-ended plastic rod which was wiped around the skin surface such that the skin was covered by a total dose of approximately 10mg/cm². The weight of formulation applied was verified from the difference in weight of the application rod and small weigh boat from which the formulation had been applied before and after dosing.

Clobetasol was allowed to penetrate into the epidermis for 72hrs after which time the remaining formulation was removed from the skin surface by washing and a single tape strip was performed to ensure that minimal 'unpenetrated' material remained on the surface of the epidermis. All washes and

tape strips were retained for quantification of clobetasol concentration. The area of epidermis exposed to the formulation was then removed from the membrane using a stainless steel punch which was cleaned with methanol between samples to avoid any cross contamination of clobetasol. Epidermal, tape and wash samples were all assayed for clobetasol concentration by high performance liquid chromatography.

Results

Figure 1 shows the fraction of the applied amount of clobetasol that was found to have penetrated into the epidermal membranes during the study. It can be clearly seen that inclusion of petrolatum in the mousse formulations has increased the amount of clobetasol penetrating into the epidermis of both intact and stripped skin samples. The recovery of the applied amounts of clobetasol in the washes, tape strip and epidermis was greater than 75% in all cases.

Conclusion

Increasing concentrations of petrolatum in topical mousse formulations containing 0.05% clobetasol was able to increase the in-vitro human epidermal penetration of the steroid in both intact and stripped skin models.

Example 3a: The Effect of Petrolatum Concentration on the Occlusivity of Topical Mousse Formulations

Aim

The aim of the study was to determine whether increasing the concentration of petrolatum in topical mousse formulations could effectively occlude the underlying skin and thereby lead to increased local hydration which in turn is known to improve the percutaneous penetration of suitable drugs.

Method

Relative degrees of occlusion of the skin in humans can be effectively quantified by following changes in the normal rate of transepidermal water loss (TEWL) caused by procedures such as formulation application. In the present study a commercially available single probe TEWL meter (Tewameter, Courage and Khazaka, Cologne, Germany) was used to determine the rate of TEWL (g/hr/m^2) at a number of $2 \times 2 \text{ cm}$ numbered test squares marked on the medial side of the forearm of a healthy volunteer. Baseline readings of TEWL were taken in triplicate at each test site prior to the application of mousse formulation at a dose of 10 mg/cm^2 containing 0, 10, 20, 30, 40 or 50% petrolatum. To ensure that the dose rate of 10 mg/cm^2 was maintained for each formulation, approximately 40mg of each mousse was weighed out onto a 2cm wide glass slide which was then used to wipe the mousse evenly across each one of the marked test squares before being reweighed to determine the total amount of mousse transferred onto the skin.

At 30 and 120 minutes following mousse application determinations of TEWL were repeated at each of the test sites. Relative changes in TEWL were then calculated by dividing the rate of TEWL following application by that taken from the same marked square at $t=0$.

Results

Figure 2 shows the actual rate of TEWL (g/hr/m^2) determined at each of the test sites prior to treatment and again at 30 and 120 minutes after mousse application. A decrease in the rate of TEWL was observed with increasing concentrations of petrolatum in the mousse formulations at both 30 and 120 minutes following application. Figure 2 clearly shows the relationship between the % of petrolatum content in each of the test mousses and the resultant relative change in the rate of TEWL determined at 30 and 120 minutes after formulation application.

Conclusion

Increasing the concentration of petrolatum in topical mousse formulations was able to decrease the normal rate of TEWL on the forearm of a healthy volunteer. The decreases in the rate TEWL observed effectively demonstrate that increasing the concentration of petrolatum in the product leads to an increase in the relative occlusivity of the topical mousse formulations tested .

Example 3b

Part 2

Aim

The aim of the second part of this study was to assess the degree of occlusivity afforded by the 50% petrolatum mousse formulation in a number of healthy volunteers.

Method

The effect of a $10\text{mg}/\text{cm}^2$ dose of 50% mousse formulation on the normal rate of TEWL was determined on the forearm of 6 volunteers in a manner identical to that described above. The relative changes observed in the rate of TEWL at 30 and 120 min after application were then compared to an untreated control site measured at the same time on the tested forearm of each volunteer.

Results

Figure 4 shows the relative rates of TEWL determined at the 2 test sites on the forearms of the volunteers. Significant decreases in TEWL ($P < 0.05$, ANOVA and Students t-test) were observed at both the 30 and 120 min post-treatment tests following application of the 50% petrolatum mousse formulation. No significant difference was observed in the rate of TEWL between the control sites over the 120 min test period ($P = 0.19$, ANOVA).

Conclusion

Application of a mousse formulation containing 50% petrolatum at a dose of 10mg/cm² significantly occluded the skin as determined by decreases in the rate of TEWL observed on the forearms of 6 healthy volunteers.

Finally, it is to be understood that various alterations, modifications and/or additions may be made without departing from the spirit of the present invention as outlined herein.

CLAIMS

- 1 A pharmaceutical aerosol foam composition including an effective amount of
of
 a pharmaceutically active ingredient
 an occlusive agent;
 an aqueous solvent; and
 an organic cosolvent
the pharmaceutically active ingredient being insoluble in both water and the occlusive agent;
the occlusive agent being present in an amount sufficient to form an occlusive layer on the skin, in use.
2. A pharmaceutical aerosol foam composition according to Claim 1, wherein the water insoluble pharmaceutically active ingredient is selected from one or more of the group consisting of an analgesic, anti-inflammatory agent, antifungal, antibacterial, anaesthetic, xanthine, sex hormone, antiviral, antipruritic, antihistamine or corticosteroid.
3. A pharmaceutical aerosol foam composition according to Claim 2, wherein the pharmaceutically active ingredient is a corticosteroid selected from one or more of the group consisting of, betamethasone valerate, and clobetasol propionate.
4. A pharmaceutical aerosol foam composition according to Claim 1, wherein the pharmaceutically active ingredient is present in amounts of from approximately 0.005% by weight to approximately 10% by weight, based on the total weight of the pharmaceutical mousse composition.
5. A pharmaceutical aerosol foam composition according to Claim 1, wherein the occlusive agent is selected from one or more of the group consisting of mineral oils and greases, long chain acids, animal fats and greases, vegetable fats and greases and water insoluble polymers.

6. A pharmaceutical aerosol foam composition according to Claim 5, wherein the occlusive agent includes petrolatum.
7. A pharmaceutical aerosol foam composition according to Claim 1, wherein the occlusive agent is present in an amount of approximately 55% by weight or less, based on the total weight of the composition.
8. A pharmaceutical aerosol foam composition according to Claim 7, wherein the occlusive agent is present in an amount of approximately 10 to 50% by weight, based on the total weight of the composition.
9. A pharmaceutical aerosol foam composition according to Claim 1, further including an effective amount of an emulsifier and/or surfactant.
10. A pharmaceutical aerosol foam composition according to Claim 9, wherein the emulsifier or surfactant is selected from any one or more of the group consisting of non-ionic, cationic or anionic surfactants, fatty alcohols, fatty acids and fatty acid salts thereof.
11. A pharmaceutical aerosol foam composition according to Claim 10, wherein the emulsifier includes a mixture of sorbitan monostearate and polysorbate 60.
12. A pharmaceutical aerosol foam composition according to Claim 9, wherein the surfactant component is present in an amount of from approximately 1 to 15% by weight, based on the total weight of the composition.
13. A pharmaceutical aerosol foam composition according to Claim 1, wherein the aqueous solvent is present in an amount of from approximately 25 to 95% by weight, based on the total weight of the composition.
14. A pharmaceutical aerosol foam composition according to Claim 13, wherein the organic cosolvent is present in an amount of from approximately 0.25% by weight to 50% by weight, based on the total weight of the composition.

15. A pharmaceutical aerosol foam composition according to claim 14 wherein the organic cosolvent is an alkyl benzoate.
16. A pharmaceutical aerosol foam composition according to Claim 1, further including an effective amount of an aerosol propellant.
17. A pharmaceutical aerosol foam composition according to Claim 16, wherein the aerosol propellant is a hydrocarbon and is present in an amount of from approximately 2.5 to 20% by weight, based on the total weight of the composition.
18. A pharmaceutical aerosol dispenser including a pharmaceutical aerosol foam composition including
- an effective amount of
 - a pharmaceutically active ingredient
 - an occlusive agent;
 - an aqueous solvent;
 - an organic cosolvent.
 - the pharmaceutically active ingredient being insoluble in both water and the occlusive agent;
 - the occlusive agent being present in an amount sufficient to form an occlusive layer on the skin, in use.
19. A pharmaceutical aerosol foam composition substantially as hereinbefore described with reference to any one of the examples.

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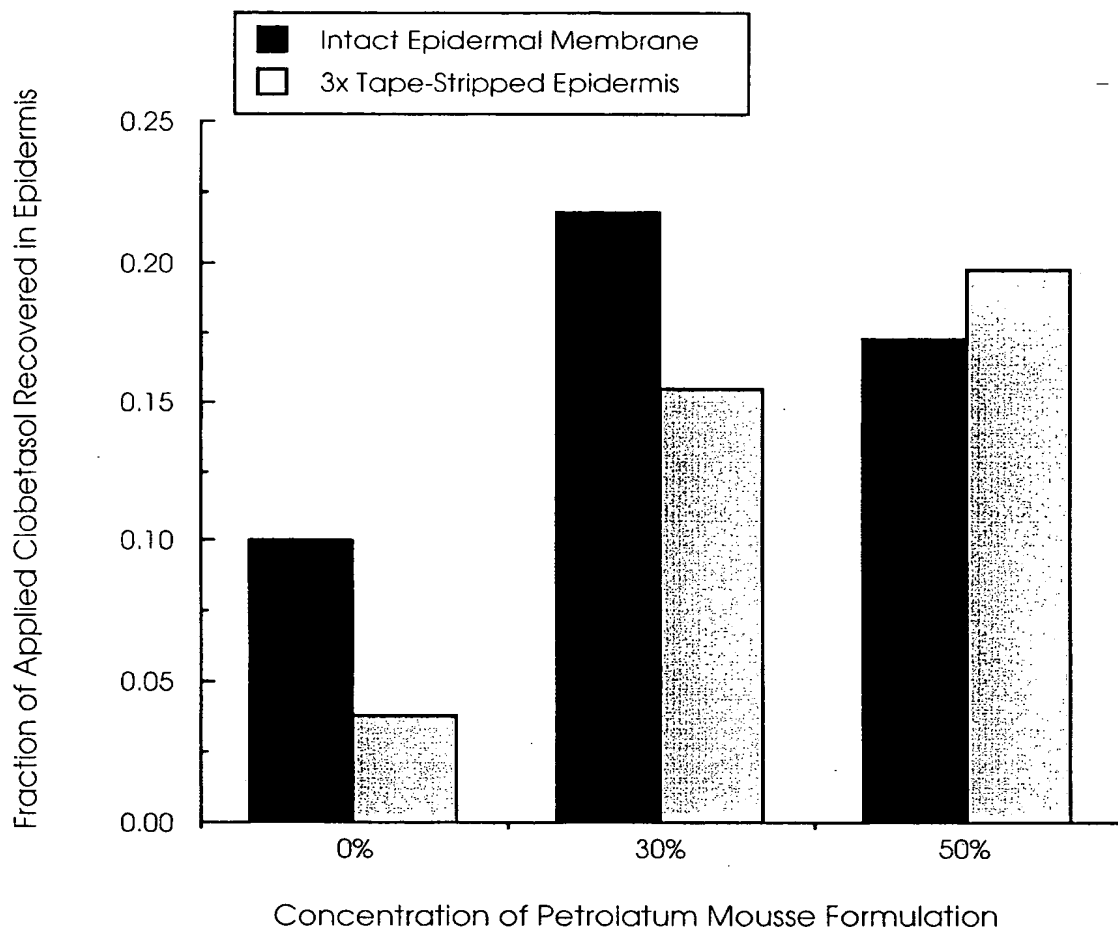


Figure 1

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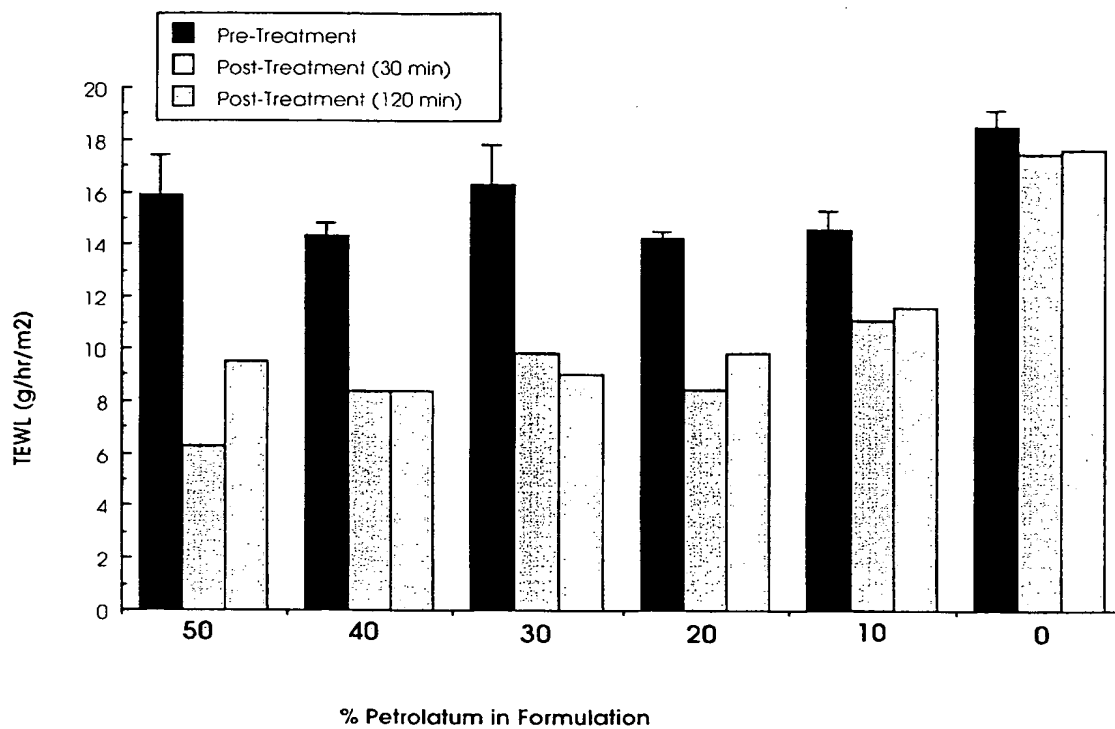


Figure 2

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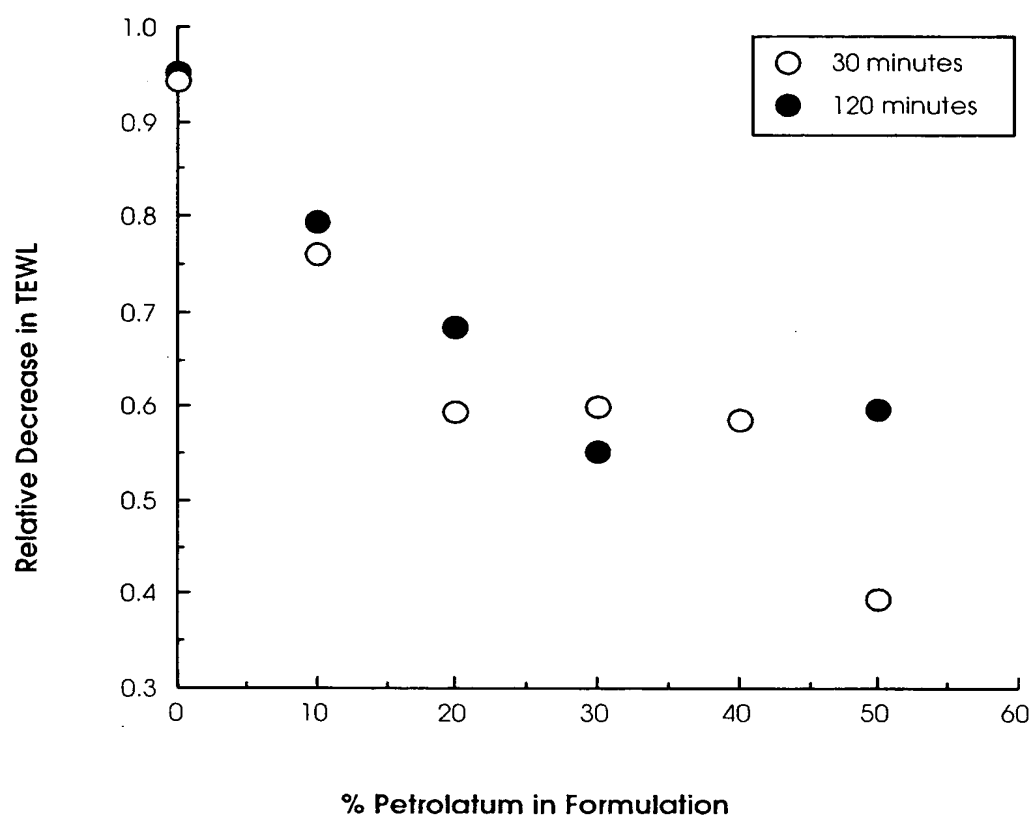


Figure 3

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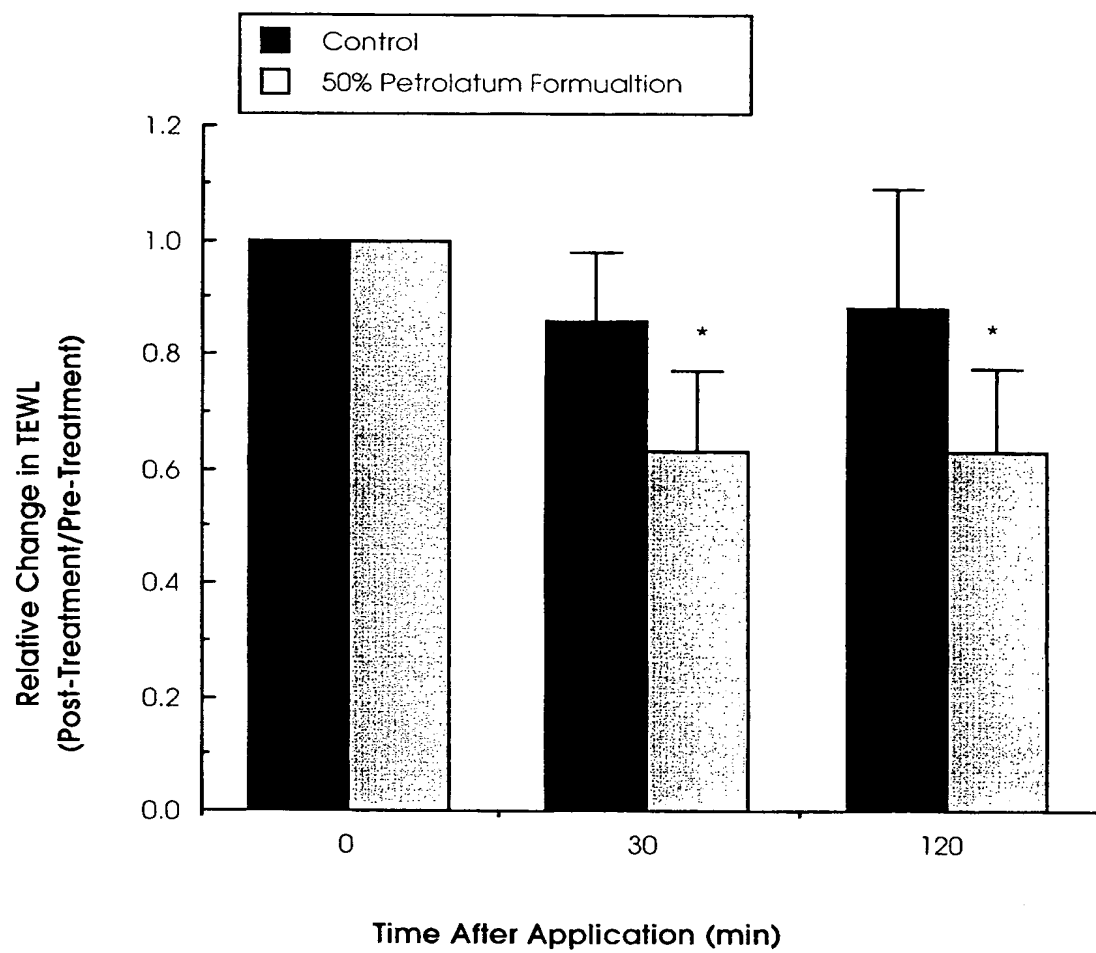



Figure 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00735

A. CLASSIFICATION OF SUBJECT MATTER												
Int Cl ⁶ : A61K 009/12												
According to International Patent Classification (IPC) or to both national classification and IPC												
B. FIELDS SEARCHED												
Minimum documentation searched (classification system followed by classification symbols) IPC A61K 009/12												
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU: IPC AS ABOVE.												
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) FILE WPAT (DERWENT ABSTRACTS) FILE CAPLUS												
C. DOCUMENTS CONSIDERED TO BE RELEVANT												
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.										
X	WO 9325189 A (Ballard Pharmaceutical Products) 23 December 1993, Pages 6-7	1-21										
P,X	WO 9904751 A (Unilever PLC) 4 February 1999, Page 16	1-21										
P,X	GB 2327344 A (Ninh Thuy On) 27 January 1999, Pages 3-4	1-21										
<input type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex												
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention											
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone											
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art											
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family											
"P" document published prior to the international filing date but later than the priority date claimed												
Date of the actual completion of the international search 14 October 1999		Date of mailing of the international search report 21 OCT 1999										
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929		Authorized officer  G.R. PETERS Telephone No.: (02) 6283 2184										

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 99/00735

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member		
W9325189	EP644753	US5143717	AU22677/92
			END OF ANNEX